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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 10/071,468 | 02/08/2002 | Stephen J. Benkovic | P05537US1 | 9968 |
| 27407 | 7590 | 11/02/2004 | EXAMINER | |
| MCKEE, VOORHEES & SEASE, P.L.C. ATTN: PENNSYLVANIA STATE UNIVERSITY 801 GRAND AVENUE, SUITE 3200 DES MOINES, IA 50309-2721 | | | SWOPE, SHERIDAN | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1652 | |

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/071,468

Applicant(s)

BENKOVIC ET AL.

Examiner

Sheridan L. Swope

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14, 15, 20, 21 and 24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14, 15, 20, 21, and 24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicant's Request for Continued Examination and the amendment, received August 10, 2004, in response to the Final Rejection, mailed March 10, 2004, is acknowledged. It is acknowledged that applicants have cancelled Claims 1-13, 16-19, 22, 23, and 25-29 and amended Claims 14, 15, 20, 21, and 24. Claims 14, 15, 20, 21, and 24 are pending and are hereby reconsidered.

Claim Rejections - 35 USC § 112-Second Paragraph

Rejection of Claims 14 and 20 under 35 U.S.C. § 112, second paragraph, is maintained. To make clear that in Claim 14, the phrase "a protease" (originally line 5, now lines 7-8) refers to the protease being assayed, as stated in the Final Rejection, said phrase should be amended to "said protease". Likewise, to make clear that in Claim 20, the phrase "protease activity" (originally line 7, now line 11) refers to the protease activity being assayed, as stated in the Final Rejection, said phrase should be amended to "said protease activity". Although Applicants state in their response (pg 4, pargs 3 and 4) that Claim 14 has been amended to recite "said protease" and Claim 20 has been amended to recite "said protease activity", said amendments have not been made. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

Rejection of Claims 14 and 15 under 35 U.S.C. 103(a) as being unpatentable over Mahajan et al, 1999 in view of Abedi et al, 1998, for the reasons explained in the First Action on the Merits, mailed September 23, 2003, and the Final Rejection, mailed March 10, 2004, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. That, neither of the cited references suggests that they be combined or that

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they be combined in the manner suggested by the Examiner. That, a person of ordinary skill in the art, looking for a means to determine whether apoptosis is associated with protease activity, would not consider a reference like Abedi, which is unconcerned with apoptosis and fails to teach the use of FRET in measuring proteolytic activity.

These arguments are not found to be persuasive for the following reasons. It is not required for either Mahajan et al or Abedi et al to explicitly suggest combining their teachings to produce the instant invention. The M.P.E.P. states that there are three possible sources for motivation to combine references: (i) the nature of the problem to be solved, (ii) the teachings of the prior art, and (iii) the knowledge of persons of ordinary skill in the art (2143.01 [R-2]). Furthermore, the courts have rejected the notion that “an express written motivation to combine must appear in prior art references....” In *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 69 USPQ2d 1686 (Fed. Cir. 2004) at 1276, 69 USPQ2d at 1690. As stated in the First Action on the Merits, Mahajan et al teach a method for assaying protease activity using a fluorescent substrate in which the protease substrate is positioned between two different fluorescent proteins, whose interaction changes if the substrate is cleaved. However, said substrate of Mahajan et al does not comprise the N-terminal portion of a single fluorescent reporter fused to a peptide substrate followed by the C-terminal portion of the reporter. Abedi et al teach a green fluorescent protein (GFP) as a scaffold for peptide substrates inserted within the GFP sequence. Faced with the nature of the problem for designing a method for assaying protease activity, it would be obvious to a skilled artisan to combine the teachings of Mahajan et al and Abedi et al to produce a GFP/protease substrate fusion protein in which the peptide substrate is inserted into the GFP scaffold and, further, to use said fluorescent protease substrate fusion protein in a method of assaying for

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protease activity. Thus, the motivation to combine the teachings of Mahajan et al and Abedi et al to render obvious the instant invention is derived from the nature of the problem to be solved and the knowledge of persons of ordinary skill in the art (M.P.E.P 2143.01 [R-2]).

It is acknowledged that Abedi et al do not teach methods for determining whether apoptosis is associated with protease activity or the use of FRET in measuring proteolytic activity. However, Abedi et al is not required to provide said teachings for the instant rejection under 35 U.S.C. 103(a) because (i) the instant claims do not recite a means to determine whether apoptosis is associated with protease activity and (ii) the use of FRET in measuring proteolytic activity is obvious over the combination of Mahajan et al in view of Abedi et al.

Rejection of Claims 20, 21, and 24 under 35 U.S.C. 103(a), as being unpatentable over Mahajan et al, 1999 in view of Abedi et al, 1998 and further in view of Martin et al, 1997 for the reasons described in the Final Rejection, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following argument. That, Martin does not relate to Mahajan and Abedi because Martin does not relate to apoptosis in enzymes that are spatially activated or protein fragment libraries using GFP, respectively. This argument is not found to be persuasive. It is acknowledged that that Martin et al does not relate to apoptosis or libraries of peptides using GFP. However, neither the role of proteases in apoptosis nor libraries of peptides comprising GFP are the specific teachings of Martin et al that render the instant invention obvious. As explained in the Final Rejection, the specific teachings of Martin et al, which remedy the lack in Mahajan et al plus Abedi et al, are (i) the importance of designing inhibitors for NS3/4A, the serine protease recited in Claims 20, 21, and 24, as a means to develop anti-viral agents and (ii) a peptide substrate that is useful for measuring NS3/4A activity. The motivation

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to combine Martin et al with the teachings of Mahajan et al and Abedi et al come from the knowledge of the ordinary skilled artisan that a protease assay developed for one particular protease could be adapted to other proteases as well. Thus, the skilled artisan would look to the art to find other proteases for which there are reasons to need a simple assay. Martin et al clearly teaches that NS3/4A fits this need and provides sufficient information about its substrate to allow the skilled artisan to adapt the assay rendered obvious by the combination of Mahajan et al and Abedi et al to the analysis of NS3/4A protease.

NEW ISSUES

Specification-Objections

On page 5, line 13, "bacterial" should be corrected to "bacteria".

Oath-Objections

The Oath of April 18, 2002 is objected to for having incomplete information regarding the claim to priority. The claim to priority recites only that the priority application is a PCT and that the date of filing is February 8, 2002. The Oath fails to provide the serial number or country code for said PCT application. A new Oath is required.

Claims-Objections

Claims 14 and 20 are objected to.

In Claim 14, for clarity and correct, grammatical sentence construction, (i) the phrase "linked to a serine protease substrate sequence" should be amended to "linked to a sequence encoding a serine protease substrate sequence" and (ii) the phrase "using fluorescence activated cell sorting (FACS)" should be set off by commas.

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In Claim 20, for clarity and correct, grammatical sentence construction, the phrase “linked to a NS3/4A serine protease substrate sequence that encodes a serine protease substrate” should be amended to “linked to a sequence encoding a NS3/4A serine protease substrate sequence”

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14, 15, 20, and 21 are rejected under 35 U.S.C. § 112, second paragraph, for improper antecedent usage.

Claim 14, line 7, and Claim 20, line 8, each recites the limitation “the serine protease substrate sequence”. There is insufficient antecedent basis for this limitation in the claim because, what is being expressed is not just the serine protease substrate sequence, but the nucleic acid construct encoding a fluorescent fusion protein comprising the serine protease substrate sequence. Clarification is required.

Claim 14 recites “protease activity” in line 11. The phrase “protease activity” on line 1 of Claim 14 provides antecedent basis. To make clear that the phrase “protease activity” recited in line 11 refers to the protease activity being assayed, said phrase should be amended to “said protease activity”.

Claims 15 and 21 recite the limitation “the amino and carboxyl-terminal fragment of...” in line 2. There is insufficient antecedent basis for this limitation. Neither Claim 15 nor 21 (or the claims from which they depend) recites an amino and carboxyl-terminal fragment of the serine protease substrate.

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Claim 20 recites the limitation “the serine protease substrate sequence” in line 8. There is insufficient antecedent basis for this limitation in the claim because, what is being expressed is not just the serine protease substrate sequence, but the nucleic acid construct encoding a fluorescent fusion protein comprising the serine protease substrate.

Claim 20 recites “protease activity” in line 11. The phrase “protease activity” on line 1 of Claim 20 provides antecedent basis. To make clear that the phrase “protease activity” recited in line 11 refers to the protease activity being assayed, said phrase should be amended to “said protease activity”.

Claim 21 recites the limitation “the serine protease substrate” in line 2. There is insufficient antecedent basis for this limitation in the claim and the claim should be amended to recite “the serine protease substrate sequence”.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F, 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.



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